REMARKS

Claims 13 and 29 have been amended to point out the invention with more particularity. Support for the nucleic acid and assistor protein in claim 13 and the influenza HA nucleic acid and full-length protein being co-encapsulated is found, for example, on page 4, lines 24-27; page 7, lines 13-14; page 7, lines 31-36; in Example 1, and throughout the specification. (This limitation was already in claim 13 in the form "said nucleic acid and said assistor protein are both associated with the same liposomes". This has simply been shorted to co-encapsulated to make the claim read more smoothly). Support for assistor protein (or the influenza HA protein) in antigenic form being displayed on the surface of the liposomes is found, for example, on page 8 of the specification, lines 4-7; and on page 19, beginning at lines 14, *et seq.* Support for inclusion of at least one cationically charged component is found on page 17, lines 11-14 and at lines 20-24.

Claims 13 and 29 have also been amended to clarify that the liposomes lack any further cell targeting moiety. This limitation is implicit in the specification as filed. None of the liposomes described or exemplified contain any targeting agents such as immunoglobulins or receptor ligands.

It is well-recognized that a feature that is inherent in the disclosure need not be explicitly disclosed in order to be claimed explicitly. For example, in *Kennecott Corp. v. Kyocera Int'l, Inc.*, 835 F2d 1419, 5 USPQ2d 1194 (Fed. Cir. 1987), claims were directed to a sintered ceramic body that explicitly required equiaxed microstructures. There was no explicit disclosure of equiaxed microstructures in the parent application from which priority was claimed. Nevertheless, priority was granted because the preparation of the same materials was described and they inherently have this property.

This is very similar to the present case where the liposomes actually prepared are free of targeting moieties. Thus, the specification inherently discloses liposomes lacking them.

Support for an infectious "agent" is found on page 12, line 21. New claim 31 is simply a counterpart to claim 27 as most of the liposomes exemplified indeed contain phospholipids. Thus, no new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention is directed to a method to administer a nucleic acid encoding an antigenic protein along with an assistor protein which share the same epitope to a mammal in such a way that a superior enhanced immune response is obtained in comparison to administering either alone. In order to do this, the two active materials are packaged into liposomes in such a way that the nucleic acid is encapsulated in the intravesicular space and the assistor protein is displayed on the surface. This arrangement protects the nucleic acid from nuclease degradation and permits the liposomes to engage the lymphocytes that are in the population primed for a humoral immune response. Further, applicants have found that it is advantageous to include a cationic component in the liposomes.

There is no suggestion in the cited Craig document (WO97/28818) or in Gregoriadis, *et al.*, *Methods* (1999) 19:156-162 that such a composition be employed. With that in mind, the following remarks are directed to the outstanding bases for rejection.

The Rejection Under 35 U.S.C. § 112, Paragraph 2

This basis for rejection is obviated by amendment. The objected-to terms no longer appear and the term "HA" has been specified in claim 29.

The Rejection Under 35 U.S.C. § 112, Paragraph 1

Applicants greatly appreciate the withdrawal of the enablement rejection previously made. This appears to be a new matter rejection.

As to the term "infectious organism", this has been changed to "infectious agent" which is supported *in haec verba* on page 12, line 21. It is also clear from the discussion in the application that such agents include both microorganisms and viruses.

The Office also objects to the phrase "said nucleic acid and assistor protein associated together and associated with liposome." Actually, this was supported on page 4, at lines 6-8; nevertheless, the claim has been clarified as set forth above.

Accordingly, this basis for rejection may be withdrawn.

The Rejection for Obviousness

All claims were rejected over the combination of Craig (WO97/28818) with Gregoriadis, *et al., Methods* (1999) 19:156-162. Applicants greatly appreciate the detailed analysis provided by the Office in responding to applicants' previous arguments. Applicants continue to believe that this combination of documents fails to teach the invention as previously claimed, but by amendment to the claims have required even further distinctions from what might be suggested by this combination.

As noted above, applicants acknowledge that Craig teaches the desirability of administering both a nucleic acid construct that will generate an antigenic peptide *in vivo* and an assistor protein which presents essentially the same antigen in protein form. Liposomes are also mentioned. However, as noted in the present application on page 3, Craig fails to teach how both the epitope-containing protein and nucleic acid should be incorporated into such liposomes. Neither does

Gregoriadis, *et al.* Gregoriadis, *et al.* simply discusses liposomal encapsulation of DNA without describing how the protein component would be included in the liposomes and displayed at the surface. This is described in detail in the present application, for example on page 35 thereof. Thus, the invention as now claimed is clearly distinct from what is taught by this combination of documents.

Craig's discussion of liposomes is quite limited. A single word is mentioned on page 12 and the only further description is on page 24 which teaches away from the invention as now claimed. Starting at line 30, Craig suggests immunoliposomes by absorbing immunoglobulins on the liposomal surface. Thus, Craig specifically teaches only liposomes which are targeted with immunoglobulin, an extraneous targeting agent not included in the claimed compositions, as the current amendment makes clear. Applicants note the comment made by the Office that the previously worded claims did not make this exclusion clear; however, it has now been made explicit. Thus, the only liposomes actually discussed by Craig are those that are targeted to the APC's.

As pointed out in the present application, and as demonstrated in the exemplified *in vivo* results, the features of the liposomal composition: 1) the nucleic acid is trapped in the intravesicular space 2) the protein displayed on its surface in the absence of a targeting agent and 3) the presence of a cationic liposome component successfully enhance the immune results obtained by this combination. There is no suggestion in the combination of Gregoriadis and Craig that these features be included in the compositions useful in the claimed methods, which contain both protein and DNA in the same liposomes.

Respectfully, applicants note that in order to obtain the actual and excellent results obtained by the present applicants, these features are required. There appears to be no suggestion in either Craig or Gregoriadis that cationic liposomes be used; Craig suggests only cationic complexes of proteins with the nucleic acids, presumably to enhance delivery of the nucleic acid to the nucleus.

As to claim 27, applicants find nothing in Gregoriadis that suggests liposomes lacking phospholipids. All of the illustrated liposomes contain at least PC, DSPC, or DOPE. Apparently PEG6000 is used in a volume reduction method, and is not even a component of the formed liposomes, much less the sole component. (See page 160, bottom of the left-hand column.)

Conclusion

Applicants believe that in light of the amendment to the claims and the foregoing discussion that claims 13, 16 and 25-31 are in a position for allowance. Passage of these claims to issue is respectfully requested.

Should minor issues remain that could be resolved by phone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 429022000800.

Respectfully submitted,

Dated: July 25, 2008

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